Elective Angioplasty Project Proposal

submitted to

Maryland Health Care Commission

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The proposed project is a randomized comparison of outcomes after percutaneous coronary intervention (PCI) performed at hospitals with and without cardiac surgery on-site. The order and content of the following submission follows the format required by the Maryland Health Care Commission. For additional detail, please refer to the Manual of Operations (version 3.0).

I. Background

Percutaneous coronary intervention (PCI) developed at tertiary institutions which had both active cardiac catheterization laboratories and active cardiac surgery programs. Initially, a significant number of PCI patients (14% in Gruentzig's first 50 cases) required emergency cardiac surgery because of unanticipated, procedure-related complications. Procedure-related complications can include abrupt closure, coronary dissection and coronary perforation. Over time, with increasing levels of operator experience, better patient selection and improved catheter and wire design, the rate of complications requiring emergency surgery declined, reaching levels of 3 to 4 % by the late 1980's and the beginning of the 1990's. With the further improvements in catheter and wire design, the advent of coronary stents and increasing knowledge regarding safe and effective antiplatelet and anticoagulation regimens and their appropriate monitoring, PCI became an increasingly safe and effective procedure. Currently, emergency CABG rates of less than 0.2% are commonly reported (1)

Arguably, today coronary perforation is the most important, life-threatening complication requiring emergency surgery. For patients treated with balloons and stents alone, current emergency surgical rates for perforation are in the range of 0.1 % (2). For patients treated with niche devices (eg. laser or rotational atherectomy, directional atherectomy, etc) and patients with high risk lesions emergency surgical rates, and complications in general, are higher (2).

The marked decline in the use of emergency cardiac surgery following failed PCI has led to performance of elective PCI without formal cardiac surgical backup in nearly all institutions (i.e. there is no cardiac operating room open, available and staffed for treating PCI-related complications). Indeed, elective PCI is frequently performed well into evening, nighttime and weekend hours, when cardiac surgical personnel are not in hospital.

The marked decline in the need for emergency cardiac surgical services and the fact that formal surgical standby is no longer practiced, have led to the idea that on-site cardiac surgery is no longer required for most patients undergoing PCI. The apparent benefits of primary PCI over thrombolytic therapy (3) motivated the extension of primary PCI capability to hospitals without on-site cardiac surgery. Based on the C-PORT Primary PCI trial (4) and other studies, several states allow primary PCI at hospitals without SOS.

Because adverse event rates are so low, and due to the success and acceptance of primary PCI at hospitals without SOS, performance of PCI in other patient groups at hospitals without SOS is gaining wider acceptance. Most registry reports (5-8) suggest that elective PCI can be performed safely and effectively at such hospitals, while others suggest low volume hospitals (less than between 50 and 100 cases per year) should not perform non-primary PCI without SOS (9). In some studies, the time to get to an operating room from the catheterization laboratory in a hospital without SOS is no longer than that required in a hospital with SOS (10). Other studies demonstrate a longer time to the operating room from

hospitals without SOS, but no difference in CABG outcome (7). Yet, despite these encouraging early results, the ACC/AHA Guidelines for performance of PCI suggest more data are needed to decide whether elective PCI can be safely and effectively performed without on-site cardiac surgery (11).

There are many motivations for performing elective PCI at hospitals without SOS. One most often heard and used in a pejorative way is the financial motivation: that is, hospitals currently without elective PCI capability want to have that capability in order to improve or maintain the hospital's 'bottom line'. But this argument, which is meant to be disparaging, is trite, myopic and can be applied to hospitals with and without SOS. For these reasons, it should be ignored as an argument for or against extension of elective PCI to hospitals with SOS. A hospital not concerned about its finances, not acting in a way to improve or maintain its fiscal well-being, is not likely to survive. Again, this is true for hospitals with and without SOS.

Other commonly-mentioned motivations for performing elective PCI at hospitals without on-site cardiac surgery include reduced bleeding (avoiding transfer of patients with intravascular sheaths in place), patient and family preference and satisfaction, physician convenience, and reduced cost (by avoiding transfer to other facilities and, potentially, additional hospital days if PCI is delayed) (6).

In addition to these not inconsequential reasons, there are deeper and more complex motivations for considering elective PCI at hospitals without SOS; motivations related to patient outcomes, access and safety.

One important motivation is to sustain primary PCI programs at hospitals without SOS. Primary PCI improves patient outcomes and reduces adverse events in patients with ST-segment elevation myocardial infarction (STEMI). Because most patients with STEMI present to hospitals without SOS, timely access to primary PCI and patient outcomes are improved by extension of primary PCI capability to hospitals without SOS. Sustaining stand-alone primary PCI programs can be difficult both financially and in terms of required human resources. The ability to perform elective PCI can help assure maintenance of these important programs and may refine expertise by increasing volume.

A second important motivation is improving access to PCI. Although there is a general consensus that most patients have adequate access to interventional services, studies which actually measure utilization of these services often find significant underutilization for patients with acute and chronic coronary syndromes who present to hospitals without PCI capability (12-15). In a 'hub-and-spoke' model of cardiac care, patients presenting to limited-care 'spoke' hospitals and who would benefit from transfer to a tertiary-care 'hub' hospital for invasive and interventional services, are frequently not transferred. This failure to utilize interventional services translates into worse patient outcomes including increased mortality and morbidity. Thus, while regionalization and centralization of services may seem like a good idea, it, in fact, may not work in the real world. Regionalization of PCI services may restrict rather than expand access to appropriate interventional care. The reasons why physicians fail to transfer patients who may benefit is unclear and is likely to be complex and multifaceted, but could include a desire to maintain care of the patient, a reluctance of the patient to be sent to an unfamiliar facility for care by unknown providers, a reluctance of the family to allow transfer to a more distant, larger and unfamiliar hospital, and probably many other reasons. The fact that frequent failure to transfer post-MI patients from spoke to hub

hospitals for revascularization is observed within the regionalized Veteran's Administration Hospital system (14) suggests financial considerations do not account for failure to transfer and underutilization. Extension of elective PCI capability to hospitals without SOS may increase access to appropriate care and reduce morbidity and mortality among patients with a variety of acute and chronic coronary syndromes.

Another motivation to study extension of PCI services to hospitals without SOS is related to improving and sustaining the quality of care at those hospitals. Because PCI has become an increasingly important part of acute and chronic coronary artery disease treatment, it is increasingly difficult to recruit and retain excellent cardiologists, both interventional and non-invasive, at hospitals not capable of providing interventional services. Lack of PCI and the creation of regional centers-of-excellence create, *de facto*, second and third tier facilities or 'centers-of-less-than-excellence'. There is a reluctance to practice cardiology in such a setting, making recruitment and retention of the best cardiologist difficult. Furthermore, because cardiology services are required ubiquitously in a hospital, failure to have excellent cardiologists can reduce the standard of care for patients on non-cardiology services. Extension of elective PCI capability to hospitals without SOS will help maintain and improve cardiology care throughout an institution, including on non-cardiology services.

Reducing 'pressure' to create additional cardiac surgery programs is another motivation to study whether co-location of cardiac surgery and PCI is necessary. From a healthcare policy standpoint, pressure to create more cardiac surgery program just to "back up" elective PCI programs is problematic, particularly since the volume of cardiac bypass procedures is flat or decreasing, even as the population at risk increases. Despite the decline in surgical case volume, the case volume of PCI continues to increase. If PCI does not require co-located cardiac surgery, then the pressure to create new cardiac surgery programs will decrease.

Irrespective of motivation, the fact is that more and more institutions are performing elective PCI without SOS in states where co-location of cardiac surgery and PCI is not required (6), and pressure to allow elective PCI without SOS continues to grow in states where co-location is required by regulation. Our national guidelines (11) continue to state that elective PCI without SOS should not be routinely performed until research clearly demonstrates equivalent safety and efficacy compared with outcomes in centers with SOS. What is required now is good scientific evidence. The universally agreed upon need for additional research in this area is, itself, among the strongest motivations for pursuing this clinical trial.

The proposed study addresses two critical and interrelated issues related to performance of PCI without SOS: 1. Can PCI be performed safely and effectively at hospitals without SOS? 2. Under what conditions is this possible? Both *what* is done and *how* it is done are of equal importance.

II. Research Design and Methods

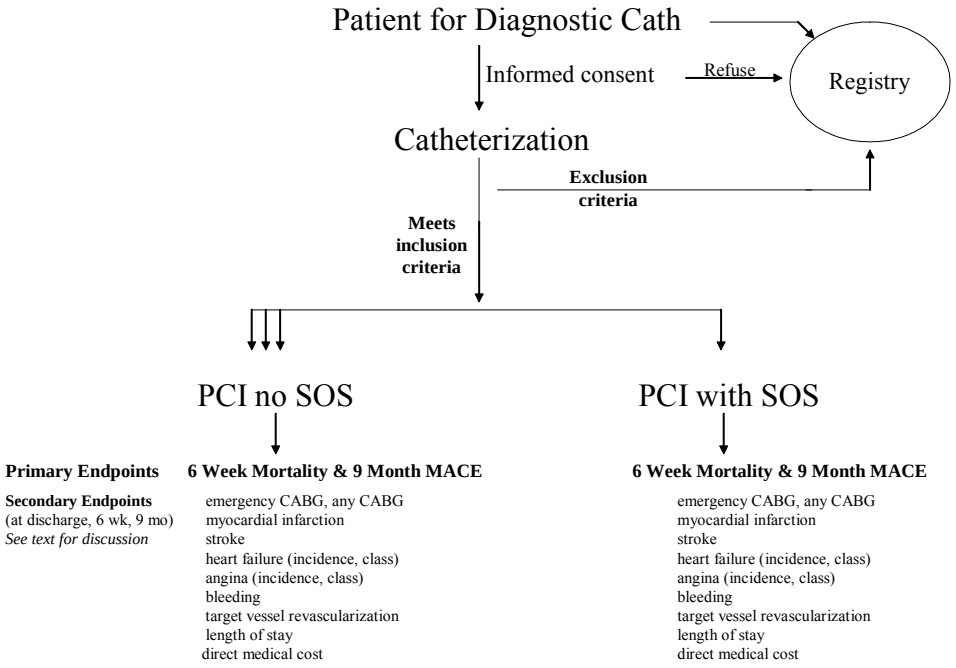
A. Study Objectives

This study tests the hypothesis that outcomes of non-primary PCI performed at hospitals without SOS are not inferior to outcomes of PCI performed at hospitals with SOS.

The **specific aims** of this project are demonstration that in patients randomly assigned to have non-primary PCI at a hospital without SOS

a. the incidence of death 6 weeks after PCI is not greater *and*
b. the incidence of major adverse cardiovascular events (MACE = death + myocardial infarction +target vessel revascularization) 9 months after PCI is not greater

than in patients undergoing non-primary PCI at hospitals with SOS. Noninferiority must be demonstrated with respect to both endpoints in order for the study's aims to be achieved.



II. Protocol A schematic of the study protocol is shown in the figure to the left. The study population consists of patients undergoing diagnostic cardiac catheterization for suspected coronary artery disease (CAD) at hospitals without SOS.

Prior to catheterization potential study subjects are approached for participation in the trial and informed consent is obtained. Subsequently, patients undergo routine diagnostic catheterization, as clinically indicated. After diagnostic catheterization and prior to randomization, post-catheterization inclusion and exclusion criteria (see below) are used to determine whether the patient can undergo PCI at the hospital without SOS. If the patient subject satisfies these criteria, then he is randomized to either remain at that hospital for PCI or be transferred to a hospital with SOS (the "usual care" group). Randomization is not symmetric but is instead 3:1, so that for every four eligible study subjects, three undergo PCI at the hospital without SOS and one has PCI at the hospital with SOS.

Patients either not approached for inclusion or who refuse to participate in the randomized trial are included in a limited data-set registry of individuals who have diagnostic catheterization at the hospital without SOS. This registry will help determine whether and to what extent selection bias occurs in the trial. Study subjects who sign informed consent but who, after catheterization, do not meet inclusion criteria or have exclusion criteria are included in a similar registry of non-randomized patients, with reasons for exclusion recorded.

Details of primary and secondary endpoint selection, data definitions and collection and analysis are below. The primary clinical endpoints are the incidence of death 6 weeks after index PCI *and* the incidence of MACE (death + myocardial infarction + target vessel revascularization) 9 months after index PCI. Noninferiority must be demonstrated with respect to both endpoints for the study aims to be achieved. Secondary endpoints include incidence of emergency coronary artery bypass surgery (CABG), myocardial infarction (MI), stroke, target vessel revascularization (TVR), any subsequent revascularization (PCI or CABG), angiographic outcomes, MACE (=death+MI+TVR), bleeding, and incidence and class of heart failure and angina, total medical costs and major resource consumption patterns. All endpoints are measured at hospital discharge, 6 weeks and 9 months after index PCI.

Two aspects of this project require special attention.

First, this is a "patient outcomes" project modeled on "Patient Outcomes Research Team" or C-PORT grants from the former Agency for Health Care Policy and Research (AHCPR – currently the "Agency for Healthcare Research and Quality" or AHRQ). These projects studied alternative standard therapies for common conditions in the "real world" practice of medicine, comparing patient outcomes (medical, economic and quality of life) that occur with those alternative therapeutic strategies. Part of the structure of such grants was to study the alternative strategies using the widest possible range of real-world practitioners and practice settings, not just tertiary or academic centers. Further, there was a deliberate attempt to minimize protocol-required care, so that how strategies were actually applied in the real-world was studied. Similarly, the C-PORT project attempts to minimize or eliminate protocol-required care. Nevertheless, in program development, which is required at all participating sites, national standards of care, so far as they exist, are applied.

Second, once randomized, patients are allocated to a strategy of care: PCI at a hospital with or without SOS. It is required as a condition of inclusion that any and all coronary artery stenoses that require treatment can be treated at the hospital without SOS. This decision is made *prior* to randomization; only when this condition is satisfied is a patient eligible for randomization. Once randomized, the patient has all required intervention either at the hospital with or the hospital without SOS for the 9 month duration of the study, with exceptions as noted below.

B. Study Design

The study is designed as a patient-outcomes oriented, un-blinded, active-control, non-inferiority trial with asymmetric randomization. Angioplasty program development (both elective and primary) is necessary at all hospitals without SOS.

1. Choice of Study Design:

Several principles guide the choice of design for this trial. First, because results of this study may influence health care policy affecting care of hundreds of thousands patients, it should furnish results of the highest quality. Second, and for similar reasons, the primary outcome measure should be both clinically meaningful and unambiguous. Third, the study should be as 'real world' as possible, with minimal or no protocol-driven care so that its application to clinical practice is as general as possible. Finally, the study must clearly define the circumstances under which PCI without SOS is safe and effective. This is done not only by clearly specifying patient, practitioner, institutional and device inclusion and exclusion criteria, but also by defining a formal PCI development program each institution without SOS completes prior to project implementation.

A randomized trial design was chosen over a registry because it furnishes the highest quality data in the most meaningful and unambiguous way. A registry offers inferior quality data because of problems common to all registry data: selection bias compounded, in this particular instance, by marked heterogeneity of the population under study. Randomization allows comparison between two groups (those undergoing PCI at hospitals with and without SOS) whose patient populations are less affected by selection bias or heterogeneity that importantly affect observed clinical outcomes.

Hospitals without SOS may have relatively low yearly PCI case volumes; compared with a registry, a 1:1 randomization scheme reduces that yearly volume by half. The asymmetric, 3:1 randomization scheme is chosen to minimize the effect of randomization on PCI volume at hospitals without SOS. This has the effect of increasing the sample size by about 25% over a more conventional 1:1 randomization scheme, but will increase the safety of the study (as there is a relationship between institutional volume and outcome) and better reflect expected real-world practice (since patient volumes at the hospitals without SOS will be reduced by only 25% rather than 50% compared with case volume in the absence of a randomized trial).

The desire to design a "real-world" study is balanced by the goal of minimizing the potential for harm. Protocol-driven care is eliminated or minimized, while patients considered at 'high risk' are not enrolled and devices associated with high complication rates are eschewed. Other study features that may minimize the potential for harm include adoption of interventional practitioner and institutional case volume minimum requirements for all participants which match the minimums set forth in the ACC/AHA guidelines.

2. Study Endpoints

Primary Outcome:

The choice of study endpoints is crucial in any trial, and is particularly so in this non-inferiority study whose outcomes may help define health care policy that can affect care of a large number of patients. Both the safety and the quality of PCI at hospitals without SOS must be non-inferior to the safety and quality of PCI delivered at hospitals with SOS.

For safety, the incidence of death and emergency bypass surgery as a result of a PCI complication are the major safety endpoints typically measured. While there are other complications that will be measured, such as bleeding, these are the two commonly considered the most critical determinants of procedure safety.

While death is an easily defined and unambiguous endpoint, the incidence of emergency CABG surgery for a procedure-related complication is more difficult to define and the implications of its occurrence (or lack thereof) more difficult to clearly understand. For example, emergency CABG rates are often lower at hospitals without on-site surgery (8) compared with their tertiary counterparts. Is this because surgery tends not to be used when not immediately available? Is this better medical care or inappropriate underutilization? Does it lead to better or less favorable outcomes other than death (eg. heart failure)? Furthermore, how well can we actually distinguish emergency CABG undertaken for non-procedure-related reasons from those undertaken because of a PCI complication; or surgery simply performed quickly because it is clinically appropriate and available within 24 hours of study entry? There is both ambiguity in the definition of "emergency CABG" as an endpoint and a potential effect of procedure location on its observed occurrence. For these reasons, although the incidence of emergency CABG will be measured, it is not included in the safety component of the primary endpoint.

Instead, death 6 weeks after index PCI is chosen as the primary safety endpoint. Mortality as an indicator of safety is measured early after the procedure, since death at a later time reflects the effect of longer-term (non-procedural) therapies and/or the natural progression of CAD.

To assess quality, the 'conventional' outcome for studies such as this is a "composite" endpoint. The composite MACE endpoint of death, myocardial infarction and target vessel revascularization (TVR) measured at 9 months after the index PCI will be used in this trial to define quality. The composite elements represent three significant adverse events which may occur as a result of natural disease progression or the overall quality of care. Assuming that the progression of disease is the same in both treatment arms, differences in the incidence of MACE reflect differences in the quality of care.

It is important to recognize that use of two primary endpoints is not a "fishing expedition": we require ***both*** endpoints to be non-inferior at the close of the trial.

Secondary Outcomes:

Secondary outcomes importantly influence interpretation the primary outcomes, assist application of study results to clinical practice and healthcare policy making, and may help generate additional hypothesis.

Secondary outcomes that will be measured at discharge, 6 weeks and 9 months include but are not limited to

a. emergency CABG
b. myocardial infarction
c. target vessel revascularization (TVR)
d. any subsequent revascularization (ASR)
e. heart failure and class
f. angina and class
g. stroke
h. composite adverse endpoint (MACE)
   MACE = death + MI + TVR
   MACE = death + MI + ASR
i. angiographic (end-procedure) complications (embolization, dissection, no reflow, etc)
j. angiographic (procedural) success (<20% residual stenosis and TIMI 3 flow)
k. completeness of revascularization
   percent of patients with complete or partial revascularization
l. bleeding (non-CABG transfusion, vascular repair)
m. length of stay
n. total direct medical cost
o. major resource consumption patterns (hospital and ICU days, surgeries, hospitalizations)

A randomly selected group of 1500 cine angiography films will be read in a core angiography laboratory (~40 films per site). This amounts to approximately 8% of the total study population. Consultation with core angiography investigators suggests that reading more films will neither sufficiently improve the accuracy nor make more meaningful the results of core lab reading to justify the added cost. The purpose of this core lab reading is to (1) determine whether the angiographic outcomes of PCI are the same at hospitals with and without SOS, (2) compare core lab readings with local physician readings of PCI procedure outcomes. Core lab elements reviewed are detailed in Chapter 18. It is not feasible to perform core lab reading on the entire patient population because of financial constraints. Therefore, relating the clinical outcomes of PCI to angiographic outcomes will not be possible for the study as a whole.

3. Sample Size

This is a non-inferiority trial. In a non-inferiority trial the expected event rate for the primary
outcome is estimated, and a margin selected which defines non-inferiority.

a. Event Rate Estimates

Event rates vary depending on the types of patients undergoing PCI. In this study, only patients with ST-segment elevation MI (STEMI) are excluded from randomization; non-ST-elevation MI (NSTEMI) patients are included in the randomized trial. Actual data from the New York State (16) and the NHLBI DYNAMIC (17) angioplasty registries are used to estimate expected event rates. Based on NYS registry data, about 29% of patients have stable angina, 63% unstable angina and 9% acute MI. Patient distribution is similar in the DYNAMIC registry.

Registry	Mortality
New York State	0.0086
DYNAMIC	0.0140
Average	**0.0113**

To estimate sample size for this trial, conservative assumptions are made. The chosen point estimate for 6 week mortality is 0.8 %, somewhat lower than the average of the observed mortality rates in the two registries (1.13 %). Note that this average (1.13 %) represents mortality at hospital discharge and is probably still lower than mortality at 6 weeks, when this component of the primary outcome is actually measured.

The estimate of MACE in this population is based on several recent drug-eluting stent trials (Table 2 below).

Table 2

MACE Definition	Rate Range (average)	Reference
All cause Death + MI + TVR, 1 year	10.9 - 13.9 % (12.2%)	Ong ATL, et. al. J Am Coll Cardiol 2005;45:1135– 41
cardiac death, MI, ischemia-driven TVR, 9 months	7 – 11.6 % (9.3%)	Windecker S, et. al. N Engl J Med 2005;353:653-62
cardiac death, MI, ischemia-driven TVR, 9 months	15 – 21 % (18%)	Stone G, et. al. JAMA. 2005; 294: 1215-1223
Cardiac death, MI, TVR 12 months	12-12.9% (12.5%)	Morice, et al, JAMA. 2006;295:895-904

Based on these data, we estimate the MACE rate (which includes *all* cause mortality) will be 12% at 9 months in this population.

b. Non-inferiority Margin

The choice of margin is difficult. While there are no hard-and-fast rules, a margin of zero, which would be choosen in an ideal world to demonstrate equivalence, is not possible in the real world because it requires an infinite sample size. For non-inferiority, some degree of "compromise", something less than this ideal, is necessary. In general, the choice of margin is determined by clinical factors. The question is "what degree of error is reasonable to allow to accept or reject the notion that one of two alternative therapeutic strategies is not inferior to the other"? Sometimes a 'relative' difference is used to estimate the proper margin. For example, if two endpoint rates differ relatively by 20% or less (with a 95% level of certainty), then we might say this difference is not clinically important. Using this principal in defining a margin, in our case, assuming mortality is 0.8%, the margin would be 0.16%. This requires a sample size of ~120,000 patients, clearly not a feasible study.

The event rate and non-inferiority margin determine sample size: the lower these rates, the greater the sample size. Sample size, in turn, determines study feasibility. In the proposed study, since the incidence of death is much lower than the incidence of MACE, sample size is largely determined by mortality.

Mortality: Sample size estimates based on a 0.8 % event rate for margins between 0.5% and 0.1% are shown in the table below. Calculations assume 3:1 randomization, one-sided test for non-inferiority using α=0.05 and β= 0.80.

Table 3

Event Rate	Margin	Sample Size
0.8 %	0.1 %	261680
0.8 %	0.2 %	65420
0.8 %	0.3 %	29076
0.8 %	**0.4 %**	**16356**
0.8 %	0.5 %	10468

There are several arguments which lead to the conclusion that 0.4% is the best non-inferiority margin to select. First, 0.4% is less than the actual observed variation in mortality between the New York State and DYNAMIC registries (see Table 1 above). Second, the margin is small, amounting to 1/250. Third, it is feasible. While a margin of 0.3% may be feasible with a sufficient number of centers performing the minimum number of PCI for a sufficiently long period of time, the 'cost' is extremely high for a minimal gain. Smaller margins are clearly not feasible. Thus, for the selected event rate and margin, 16356 subjects are required.

MACE: Since the expected MACE rate is more than 10-times higher than the expected mortality, this measure of quality and longer term outcome can have a larger absolute margin. For a 12% MACE rate, a difference between MACE rates at the alternative PCI locations of 1.8% or less is considered clinically insignificant.

With 16356 patient-subjects, there is 92% power to define non-inferiority at this level.

c. Study Sample Size

With two primary endpoints, overall study power is conservatively estimated as the product of the power of each endpoint at a given sample size. Thus, although the power to detect mortality with 16356 patient subjects is 0.80 and the power to detect MACE is 0.92, the overall study power is 0.74. To achieve a power of 0.80, a sample size of approximately 18360 patients is required (no SOS = 13770, SOS =4590). The study sample size will be 18360 total subjects.

C. Data Analysis:

The main objective is to assess the non-inferiority of PCI at hospitals without SOS versus PCI at hospitals with SOS.

a. Primary Outcomes:

The primary analysis will test the null hypothesis of inferiority in either or both endpoints:

H0: Mortality rate at 6 weeks for hospitals without SOS >= Mortality rate at 6 weeks for hospitals with SOS + .4%
OR
MACE rate at 9 months for hospitals without SOS >=MACE rate at 9 months for hospitals with SOS + 1.8%

against the alternative composite hypothesis of noninferiority

HA: Mortality rate at 6 weeks for hospitals without SOS < Mortality rate at 6 weeks for hospitals with SOS + .4%
AND
MACE rate at 9 months for hospitals without SOS < MACE rate at 9 months for hospitals with SOS + 1.8%.

Rejecting H0 in favor of HA will constitute success in achieving the trial's primary aim

The hypothesis for the primary aim will be tested by calculating 95% one-sided confidence intervals for differences in 6-week mortality and 9-month MACE rates and determining whether both exclude .4% and 1.8%, respectively. If they do, then the alternative hypothesis of joint noninferiority will be accepted. These confidence intervals will be based upon asymptotic normal approximations to the estimated rates; our simulations have shown that
the approximations are close and produce false positive rates very close to the specified 5%.

All analyses will be performed on an intention-to-treat basis.

Outcomes analysis will be performed for several pre-defined subgroups. Those are (1) clinical presentation (ACS vs Elective), (2) diabetes (present, absent), (3) gender, (4) age > 70 vs age < 70, (5) normal vs abnormal renal function (creatinine < 2 mg/dl vs $\geq$ 2 mg/dl).

b. Secondary Outcomes:

A number of analyses of secondary endpoints (see secondary endpoints above) will be conducted at the 6 week and 9 month endpoints.

Univariate logistic regression analysis will be performed to estimate crude odds ratios and corresponding 95% confidence intervals for binary (yes/no) secondary outcomes. Multivariate logistic regression will be used to adjust for potential confounding factors. Odds ratios are considered to be statistically significantly different if their 95% confidence intervals do not include 1. For continuous outcomes, analagous univariate and multivariate least squares regressions will be conducted. All analyses will be performed on an intention-to-treat basis

For the economic analysis, for testing of discrete variables, chi square tests or Fisher's exact tests will be used. For testing of continuous variables, nonparametric statistical tests will be used, such as the Wilxcoxon rank-sum test.

The mean between-treatment-group differences in medical costs based on 1000 bootstrap datasets will be estimated, and estimate a 95% confidence interval (CI), and calculate the percentage of samples in which PCI in a non-SOS facility is cost-saving versus PCI in a SOS facility. The primary analysis will use a societal perspective, although all costs are not included.

c. Crossovers:

Since the study continues for 9 months, it is the intention of the study to keep patients in the same treatment group throughout the 9 month study duration. The likelihood of succeeding in keeping patient subjects within their treatment allocation is very high for a number of reasons. First, patient subjects are cared for by their local healthcare providers: their 'study' physicians are their local physicians. Second, patient subjects are likely to return to these local providers and to their local community hospital for any required subsequent care, since they selected those physicians and that institution initially. Third, patients may only have PCI at a hospital without SOS as part of the C-PORT project: thus, patients initially randomized to PCI at the hospital with SOS must have PCI at that site, since PCI at the hospital without SOS violates healthcare regulations (except when performed in accordance with the C-PORT study).

These study intentions may be modified as the 'real world' dictates: thus, if a patient initially treated at one type of institution, presents with an acute STEMI at the alternate institution, then emergent removal to the presenting hospital catheterization laboratory should occur without regard to initial treatment allocation. Similarly, if a patient presents to a hospital in another locale (e.g. during travel) and requires revascularization, the patient and local physician may decide that revascularization at the hospital to which he is currently admitted is in the patient's best interest. Finally, if a patient-subject allocated to PCI at a hospital without SOS needs a subsequent revascularization that requires use of a niche device

(e.g. rotational atherectomy) not available at the hospital without SOS, then, the patient will have that revascularization at the hospital with SOS. While literally 'crossovers', these are events that can and will occur in the real-world application of PCI at hospitals without SOS.

All primary analyses will be by intention-to-treat, with the extent, timing (initial therapy versus during follow-up) and reasons for 'crossover' noted.

D. Feasibility

We anticipate enrolling approximately 40 participating sites. Assuming 40 institutions are involved and that each performs 200 PCIs per year, then 16000 patients can be recruited in two years and 18360 in 28 months. Since many centers will perform more than the minimum number, recruitment time may be shorter.

For the two states with the largest number of participating sites, New Jersey (9 sites) and Georgia (10 sites), the average *current* diagnostic cardiac catheterization case volume is in excess of 800 per year. At every institution, this case volume represents a *minimum* volume, as a significant number of cases are sent directly to a tertiary facility for diagnostic and possible therapeutic catheterization; these cases may augment the current case volume. If 30% of diagnostic catheterizations are amenable to PCI, then on average, each site could have in excess of 240 PCI cases per year.

In the one pilot program running in Alabama, of 208 patients approached for enrollment, 205 signed informed consent (98%).

III. Protocol for including patients in the study: Patient inclusion/exclusion criteria and consent procedures

A. Patient Eligibility

Study Population The patient population includes inpatients and outpatients undergoing diagnostic cardiac catheterization for suspected coronary artery disease (CAD) at hospitals without SOS.

Patient *inclusion* criteria are

Pre-catheterization

1. must be undergoing diagnostic cardiac catheterization for suspected CAD
2. be at least 18 years of age
3. must not be pregnant (negative pregnancy test) or must not be of childbearing potential
4. must be able to give informed consent.

Post-catheterization

5. coronary artery disease judged to be clinically and angiographically significant

6. ability to perform PCI with equipment available at the local site (see below)
7. procedure risk judged to be not high (see below)

Patient *exclusion* criteria are

Pre-catheterization

1. inability to give informed consent
2. ST-segment elevation myocardial infarction
3. pregnancy

Post-catheterization

4. high likelihood of requiring a device not available at the hospitals without SOS (see below)
5. no need for PCI
6. need for coronary artery bypass surgery
7. high procedural risk (see below)

High procedural risk criteria are

1. PCI of unprotected left main coronary artery
2. PCI of left circulation lesion in the presence of critical (>70%) unprotected left main coronary artery lesion
3. poor left ventricular function (EF≤ 20%) *and* need to perform PCI in a vessel supplying significant myocardium

B. Patient Identification

The intent of the project is to identify and approach for study participation all consecutive patients presenting to participating hospitals for diagnostic catheterization for suspected or known coronary artery disease.

Responsibility for identification of patients that may be candidates for the trial rests primarily with catheterization laboratory staff, although this may vary from institution to institution. All patients undergoing diagnostic catheterization not approached for participation or who refuse to participate will be included in a limited data-set registry. The purpose of the registry is to define characteristics of patients who did *not* participate in the study so that selection bias can be identified and defined.

Once a patient is identified (meets all inclusion criteria and has no exclusion criteria), the patient undergoes diagnostic cardiac catheterization. If the patient does not require revascularization, requires revascularization not available at the no-SOS hospital (either PCI with a device not available or CABG), or is judged high risk (see above), then the patient is not randomized. Patients excluded from participation after catheterization and who are not randomized, will be included in a registry.

C. Informed Consent

Informed consent must be obtained prior to diagnostic catheterization on all study patients. Verbal consent or consent obtained during a cardiac catheterization is not allowed. Informed consent must be obtained at the hospital where catheterization takes place and requires IRB approval of that institution.

The individual obtaining informed consent must be approved and listed with the local IRB. Generally, this will be the invasive cardiologist performing the diagnostic catheterization. The entire consent must be explained to each patient in detail and the patient must have sufficient time to review the consent, ask questions about the study and have those questions answered by individuals authorized by the local IRB to do so, and to consult with any other individuals they may require in order to make an informed decision regarding participation. In the case of potential study-subjects who may not fully understand English, a translator must be provided to review the consent in detail, be available to allow discussion between the investigator-physician and the potential study-subject, and be available for any individuals the potential study-subject may wish to consult during the consent process. In the case of individuals considered not mentally competent or for reasons other than language are unable to give informed consent, surrogate consent may be obtained if and only if specifically allowed by the local IRB for this study from individuals (e.g. next of kin, power of attorney) authorized by the local IRB.

The consent may be translated into other languages if approved by the IRB.

There may be separate consents for the research study and for the procedure (standard procedure consent currently in use at the participating institution). Alternatively, a single consent may be used if approved by the local IRB. All required elements of the standard procedure consent must be incorporated into the research consent if a single consent is used. This includes but may not be limited to information regarding conscious sedation, potential for blood product transfusion and exceptions to anesthesia.

All aspects of the informed consent must be reviewed and considered in detail by potential study-subjects. Patients will be informed of all the usual risks, benefits and indications for catheterization and possible PCI, the study protocol and its risks, potential benefits if any and alternatives. It is particularly important that the study subject know that (1) this is a research study, (2) elective PCI without SOS is not allowed in this State except as part of this study, (3) elective PCI is usually performed in hospitals with SOS because emergency heart surgery is sometimes required because of a procedure-related complication, although this is rare (about 1 to 2 per 1000 cases), (4) if they do require surgery, there is a plan in place for emergency transfer, (5) there is no guarantee they will have PCI at the participating hospital because CABG may be the best option for them, or because they are considered by their physician at 'high risk' for a complication, or if they require treatment not available at the participating hospital: in that case, they will be transferred to a tertiary hospital for additional care and will not be randomized, (6) their

medical information and the cost of their care including medical bills will be shared with researchers involved in the study, but will be kept strictly confidential.

Informed consent must include a statement of conflict of interest related to the institution (hospital facility) and, if applicable, the practitioner (interventionalists). The institution may derive financial benefit from a participant's enrollment, and this must be explicitly stated in the informed consent. Furthermore, when the physician-practitioner may benefit financially if the patient participates in the study (eg. if the patient does not participate, then PCI is done by another physician and the physician-investigator does not bill for the PCI procedure; or if the physician has a financial interest in the hospital such that if a patient has a procedure at that institution and that institution derives financial benefit, then the physician-investigator may also financially benefit), then that must also be explicitly stated in the informed consent.

Signed consents must be copied and the original placed in the patient chart, and a copy given to the patient and one kept for study records. In addition, signature pages for all consents are entered into the Sextant database and associated with the study registration case report form.

All individuals obtaining informed consent must be approved by their local IRB and must complete all required courses in informed consent procedures, HIPAA issues and human investigation as required by the local IRB. It is strongly encouraged that all principal investigators, all co-investigators and all research nurse coordinators complete the NIH-sponsored online course in human subjects protection available free of charge at http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp.

IV. Need for Institutional Review Board Review

Every participating site must have an identified principal investigator, identified co-investigators, a study coordinator and must have its own IRB approval prior to initiating patient recruitment. The materials (background, study design, risks, benefits, consenting procedures and consent form) for each individual hospital will be modeled after materials submitted to and approved by the Johns Hopkins IRB.

This study has been approved by the Johns Hopkins Medical Institutions IRB and by multiple IRB's at participating institutions including the Duke IRB, Western IRB and many local IRB's..

V. Criteria for participating hospital sites and physicians

In addition to patient inclusion and exclusion criteria, there are institutional, physician and device criteria for participation.

A. Participating Site Inclusion Criteria

Participating sites are required to enter into a formal contractual arrangement with the Clinical Coordinating Center. This agreement includes financial arrangements between the participating site and the Clinical Coordinating Center related to program development and data collection, and details work the Clinical Coordinating Center performs for the participating site.

Participating sites must meet the following inclusion criteria:

1. capability of performing a minimum of 200 PCI's (elective + primary) per year in an existing laboratory (this may be modified by specific State requirements)
2. agree to complete an elective PCI development program (and a primary PCI development program if not already completed)
3. agree to abide by the study protocol and to physician, patient and device selection criteria defined in the Manual of Operations
4. agree to collect and transmit study data in a timely fashion
5. agree to develop and maintain a quality and error management program, including a weekly interventional conference and monthly QE review
6. perform primary PCI 24/7
7. develop and maintain necessary agreements with a tertiary facility (which must agree to accept emergent and non-emergent transfers of enrolled patients for additional medical care, cardiac surgery or intervention)
8. develop and maintain agreements with an ambulance service capable of advanced life support and IABP transfer that guarantees a 30-minute-or-less response time
9. except as provided by alternative State regulation, there must be a proven, practiced plan for removal of a patient from the hospital without SOS to a hospital with cardiac surgery within 60 minutes of initiating the call for emergency transfer (exceptions may be made for certain, particularly rural, settings)

B. Participating Physician Inclusion Criteria

Interventionalists who wish to participate in this project must meet the following criteria:

a. meets the ACC/AHA standards for training and competency (minimum of 75 cases per year)
b. agrees to practice in accordance with the study-defined device and patient selection criteria
c. agrees to obtain necessary informed consent for patient participation in this project
d. agrees to necessary data form completion
e. agrees to participate in the elective (and primary, if necessary) development program

f. agrees to abide by the study protocol defined in the Manual of Operations
g. agrees to participation in the QE management program
h. agrees to participate in the weekly interventional conference

C. Device Selection Criteria

The following devices will be excluded from use:

1. any atherectomy device
    a. rotational atherectomy
    b. directional atherectomy
    c. laser atherectomy
    d. excisional atherectomy
    e. use of cutting balloons except within stents for in-stent restenosis

VI. Data collection and management plan

General categories of data to be collected on all patients is summarized in Table 4. Data element definitions will conform to the ACC NCDR Data Definitions v 3.04.

Table 4

Data Category	Examples
Demographics	Gender, race
Cardiac Risk Factors	Diabetes, hypetension, smoking
Cardiac History	Prior MI, CABG, PCI
Index Laboratory Studies	Creatinine, ECG, CK, troponin
Diagnostic angiography	Disease severity and extent
PCI procedure	Devices, medications, outcomes
Outcomes	Death, MI, CABG, stroke, bleeding
Medications	With PCI, after PCI
Angiographic Core	Pre, Post Stenosis severity, TIMI flow
Economic	Hospital cost, physician cost

Data Gathering Responsibilities

Participating site study coordinators (at hospitals without SOS) have sole responsibility for gathering and entering data into the Sextant data management system. No individual at any affiliated tertiary hospital with SOS or any other healthcare facility or provider enters data into the database at any time. This means that all data coming from all sources, including hospitals to which study subjects are transferred is gathered by the participating site study coordinators (at hospitals without SOS).

Data will be gathered at the local site and entered into the Sextant data management system. Data are entered in two ways in Sextant: (1) completion of web-based case report forms and (2) scanning or attaching of required supporting documentation into the database.

Case Report Form (CRF) Completion

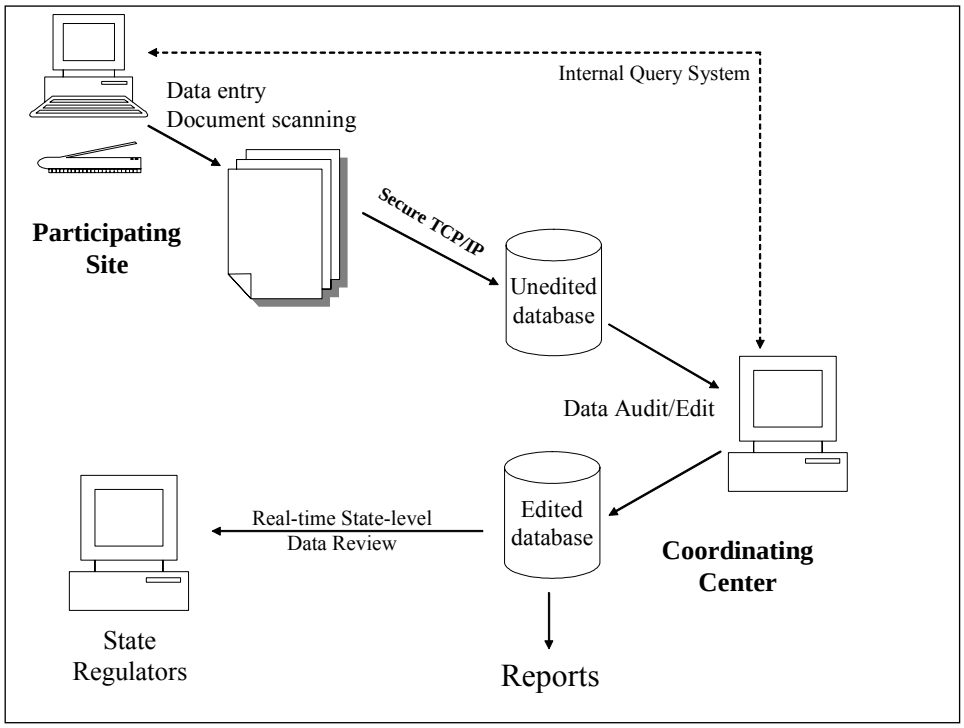
The "index hospitalization" includes hospitalization for the index procedure until the time of discharge from either the hospital without SOS or from the hospital with SOS if the patient was transferred to that hospital for *any* reason. CRF's related to the index hospitalization will be completed within 72 hours of patient discharge and will include data and outcomes from all sources.

Follow-up CRF's are completed by telephone interview at 6 weeks, 3, 6 and 9 months.

Event CRF's for any event occurring during initial hospitalization or during the 6 week, 3, 6 and 9 month follow-up period must be completed within 72 hours of occurrence. Events include but are not limited to death, myocardial infarction, stroke, bleeding, subsequent angiography or revascularization (PCI or cardiac surgery).

All data are entered into the Sextant data management system (see below) using web-based CRF's and scanning into the database any required supporting documentation appropriately censored of any private health information.

Data Gathering Instruments: Participating hospital staff will enter data in Sextant, a data management system. Sextant data flow is shown schematically in the accompanying figure.



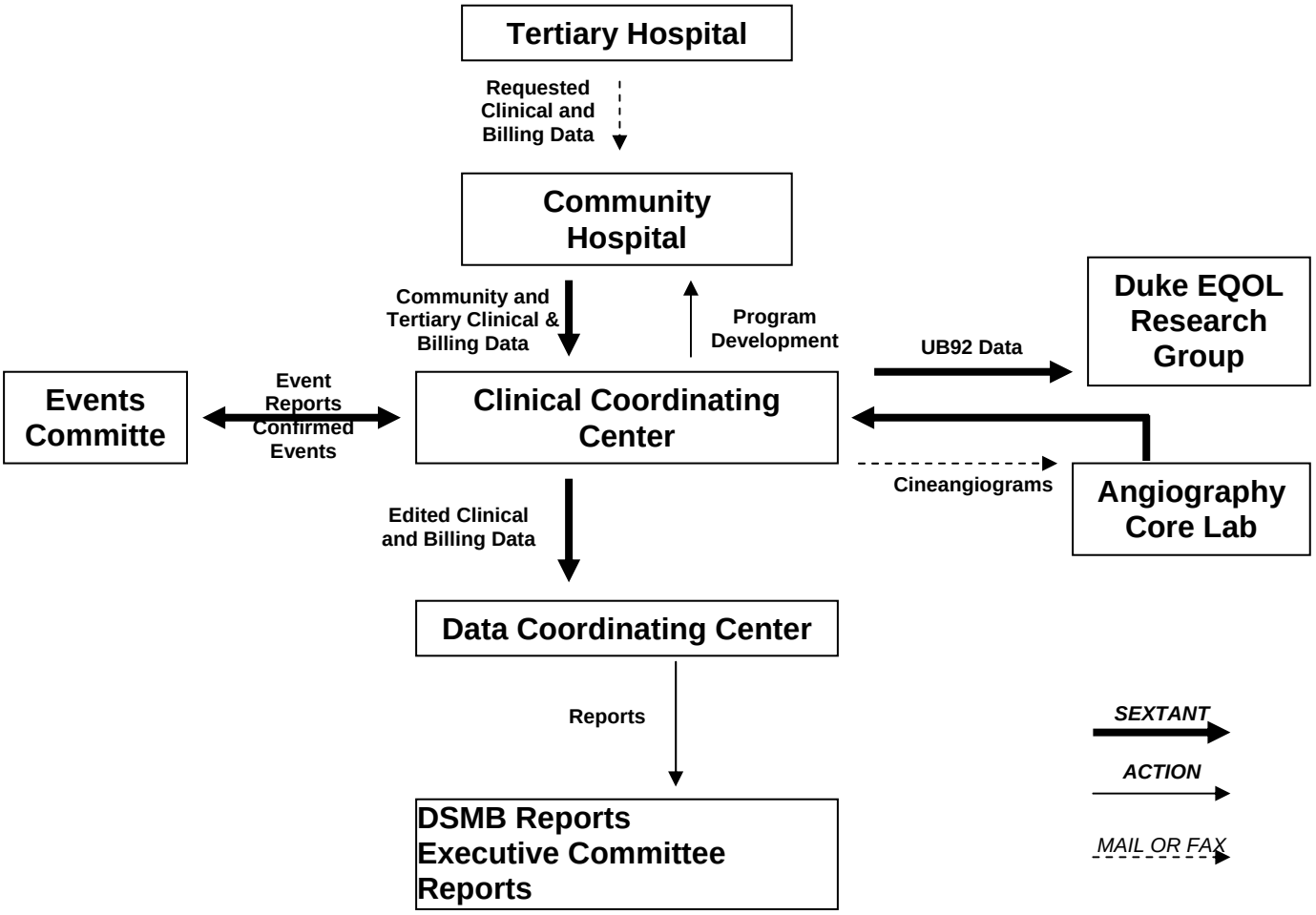
Data are entered on electronic CRF's. CRF's include alphanumeric text entered into fields and may also require attachment (scanning or drag-and-drop) of associated supporting documentation. For example, the Registration CRF requires scanning in the signature page of all informed consents. Once scanned into the database, the signed informed consent signature page is permanently associated with the Registration CRF. The Initial Hospital Data CRF requires scanning in of certain laboratory

report sheets (e.g. documenting serum creatinine prior to catheterization). Once completed, CRF's and their scanned supporting documentation is locked by the participating site coordinator and sent to the Coordinating Center for review. Data resides at this point in an 'unedited' database. Data in the unedited database are reviewed for completeness and for accuracy. If there are questions regarding a particular CRF, an internal query system allows communication between Coordinating Center and Participating Site personnel so that these issues can be resolved. CRF's can be unlocked for correction by Participating Site personnel, if appropriate. Once audited and edited as needed, data are 'certified' and permanently locked in an edited database.

Reports can be generated from the edited (and unedited) database for review (e.g. by the DSMB). In addition, State regulatory authorities can have real-time, State-level data for review from any and all sites within their State for use in on-going quality assessment. These data are devoid of any private health information (e.g. demographics).

Participating site personnel have access to their own local data through Sextant, as well, enabling creation of reports for quality assurance purposes throughout the study.

Overall Structure: The overall structure and data flow for proposed trial is depicted schematically in the picture below.



Each participating hospital assigns data collection duties to one or two clinical study coordinators. These individuals are responsible for completing case report forms, copying relevant parts of the documentation including consents and required parts of the medical record, and storing these locally. Each participating hospital identifies a economic study coordinator. This individual is responsible for gathering all required billing information.

In addition, the clinical and economic study coordinators are responsible for obtaining required data from tertiary hospitals to which the patient subjects are transferred during initial hospitalization and during the 9 months of follow-up. No case report forms are completed and no data are gathered by staff at the tertiary hospitals: all data gathering, form completion, data storage and data transmission are done by the study coordinator(s) at the hospitals without SOS to which the patient initially presents.

A. Clinical Coordinating Center

The Clinical Coordinating Center for the project is at the Johns Hopkins Medical Institutions. Coordinating center procedures are described in what follows.

The primary functions of the Coordinating Center are

1. project design
2. project implementation and execution
3. participating site development, implementation and execution procedures
4. deployment and maintenance of project data management tools (Sextant)
5. cooperative interaction with State agencies (Departments of Health)
    a. obtain waivers for project participation
    b. regular outcomes review
    c. provision of real-time, patient-subject outcomes data for State monitoring
6. angioplasty development program design and implementation at participating sites (see Manual of Operations)
7. development, implementation and coordination of project Committees that include
    a. Data and Safety Monitoring Board
    b. Events Committee
    c. Substudy Committee
    d. Publications Committee
    e. Steering Committee

Participating Site Personnel Staff Training

All study personnel involved in data collection will be trained by supervisory personnel (principal investigators and senior nurses) before beginning actual data collection.

Data Handling Procedures

The CPORT organizational structure for this trial is shown in the figure above. Clinical and economic data are sent to the Clinical Coordinating Center from two field sources: the community hospital (without SOS) and the tertiary hospital. These data (case report forms and required supporting documentation) are reviewed by Clinical Coordinating Center staff. If data are correctly entered along with required supporting documentation then that record (study form) is certified (and locked) and sent to the Data Coordinating Center.

Angiograms are sent directly to the Angiographic Core Lab from the participating sites. The angiograms are reviewed and data are entered directly into Sextant database. The Clinical Coordinating Center reviews entered data and certifies it as complete before forwarding the data to the Data Coordinating Center.

Missing data reports can be created locally (at the participating site) in Sextant. Queries can be created for specific case report forms within Sextant, as well.

Reports for Committees (eg. the DSMB) are created through Sextant by the Data Coordinating Center.

Patient identification data will be kept on a separate form within Sextant, with the patient study identification code providing a link between that code and the patient's identity. ***All patient information data are kept strictly confidential.*** Access to medical records and any study database is on a need-to-know basis only and can be restricted within Sextant to certain individuals. Access to Sextant itself is username and password protected and all activity is kept in a permanent audit log.

Copies of data forms and records will be stored at the participating hospitals, as well. These data will be placed in a folder for each patient.

Study Staff On Call

A study physician will be on call at all times to answer questions that may come up in the course of the trial. This physician-investigator can be reached through the **C-PORT trial principal investigator study pager number: 1-410-283-3660.**

Elective PCI Development Program

An elective PCI development program is being implemented as part of this project. Some of the methods and content are taken from the current C-PORT primary PCI development program, but additional resources are required. The program outline includes the setting of standards (for practitioners, institutions, facilities, care and staff competency), training of staff (observational, didactic and hands-on as required), development of logistics (particular attention to development of formal tertiary hospital

and EMS affiliations for patient transport) and development of a quality and error management program (consisting of data collection and review, monthly staff QA meetings and weekly M&M in a cath conference setting, development of credentialing criteria).

Formal agreements between the participating site and both a tertiary facility willing to receive and an ambulance company capable of transporting any study subjects requiring emergency transport for tertiary-level care for any reason. A proven plan must be in place for emergency transport of a study subject from a hospital without to a hospital with SOS within 60 minutes of a call for such transport. The plan must be practiced and documented every 6 months.

Similarly, an important element of the program is related to minimizing the risk of coronary perforation and minimizing its impact should it occur (see Appendix materials). To this end, all participating facilities and practitioners will be required to train for use of the JoMed covered stent. In addition, all participating physicians will learn how to occlude distal coronary perforations using embolization techniques (coils, glue, etc). Alternatively, interventional radiologists may be available to assist the interventional cardiologist in embolizing distal coronary perforations. The plan of action for managing perforations including ambulance transport, operating room notification, reversal of anticoagulation, periocardiocentesis techniques, and use of sealing technologies (covered stents and embolization techniques) will be written, detailed and practiced every 6 months. Competency will be maintained by twice-yearly review and retraining.

Protocol: The project will require approval of each participating institution's IRB. Informed consent specific to this protocol will be obtained from each participating patient.

A requirement of all centers will be completion of a formal elective PCI development program.

In keeping with a patient-outcomes oriented project, there will be no or minimal protocol-required care. Application of institution, physician, device and patient selection criteria, data collection and informed consent are the only study requirements. Patients will be identified as potential candidates by matching with pre-specified inclusion and exclusion criteria. The principle or co-investigator will obtain informed consent from the patient. Two clinical data collection personnel will be trained to collect, enter and transmit clinical data, both case report forms and any required supporting documentation from the medical record. Similarly, two billing coordinators will be trained to submit billing information.

PCI will be performed and conducted by the interventionalist, with no protocol-required care. The only limitations are those imposed by the available equipment, which itself is selected as described above.

Study Committees

Steering Committee
Executive Committee
Operations Committee
Event Committee
Publications Committee
Data and Safety Monitoring Board

The Steering Committee will be made up of Principal Investigators from each of the participating centers as well as outside experts in the fields of cardiology and clinical trials. The Executive Committee will be a subset of the Steering Committee has been meeting for two years and supervised the develop of the current study protocol. The Operations Committee will be a subset of the Steering Committee handling day-do-day operations of the clinical trial. Except for the Data and Safety Monitoring Board (DSMB), committee membership may include participating or non-participating investigators, physicians, nurses and others involved in the C-PORT trial.

The DSMB consists of physicians, clinical trial specialists and at least one statistician and one bio-ethicist. The roster of the study DSMB is attached to this Manual of Operations, as are its bylaws. The DSMB is in place for this project and held its first meeting November 8, 2005. At that meeting bylaws were approved and the study project design was also approved.

Emergency meetings of the DSMB may be required to review major adverse events, particularly death, that may be procedure-related. These emergency meetings will require a quorum of the DSMB and will be conducted via conference call.

The Event Committee is charged with reviewing all potential major adverse outcomes including death and emergency CABG. Particularly for death and CABG within 24 hours of a procedure, the Event Committee will be required to adjudicate whether the death was definitely, probably or possibly related to participation in the project or the procedure, itself. All such events will be adjudicated by the Events Committee within 72 hours. Adjudication requires review and disposition of 2 members; if there is a difference of opinion regarding adjudication, a third member will review and all three reviews will be considered by the Event Committee Chair or Associate-Chair who will make a final determination. That final determination will be sent to the Chair of the DSMB who will, in turn, decide whether an emergency meeting of the DSMB is required. The meeting will be completed and the adjudication reviewed within 72 hours of the Event Committee determination. The DSMB will recommend either continuation of the trial, continuation of the trial but require additional review, suspension of the trial permanently or for additional review, suspension of trial activity by a specific site or practitioner, or any other action it deems appropriate in response to the event.

B. Data Coordinating Center

The Data Coordinating Center is the Maryland Medical Research Institute (MMRI), which worked with the Clinical Coordinating Center on the first C-PORT project (a randomized comparison of thrombolytic therapy and primary PCI at hospitals without SOS). Dr. Bruce A. Barton and Ms. Sandy Forman, along with other MMRI staff, will perform a number of services for this project. These services include:

1. Develop the randomization schedules for each clinical site and implement the schedules in MMRI's 24/7 randomization system (ATRS)
2. Develop the analysis plan for the study, including interim monitoring, contents of the DSMB reports, and the analysis strategies for primary and secondary outcomes;
3. Receive and process data routinely from the Clinical Coordinating Center for safety reports and DSMB reports;
4. Based on the analysis plan, program the DSMB reports, and present the reports to the DSMB;
5. Develop interim monitoring bounds and present those bounds to the DSMB for discussion;
6. Perform the final analyses for the study, based on the analysis plan;
7. Develop the material and sections needed for the main results manuscript; and
8. Interact with the Clinical Coordinating Center regarding data integrity and completeness issues.

Interaction between the CCC and DCC is facilitated by a number of factors. First, there is a long history of collaboration on similar projects in the past. Second, the sites are located in the same city (Baltimore, MD). Third, the data collection infrastructure is built upon Sextant, a multicenter clinical trial data management system which is web-based and paperless, making receipt and access to all data simple and rapid.

C. Duke Economics and Quality of Life Center

Dr. Eric Eisenstein (D.B.A.) is the principal investigator, Linda Davidson-Ray, MA is project leader and Kevin Anstrom, PhD is the lead statistician. Daniel B. Mark, MD, MPH will provide study oversight at Duke.

The Duke EQOL Coordinating Center is charged with entering Medicare Cost Report information, applying the appropriate Medicare Fee Schedule charge to physician and technical services and analyzing the economic data. Data entry is performed by the local billing coordinators at each participating site.

Sextant, the multicenter clinical trial data management system described above facilitates interaction between the CCC, DCC and Duke EQOL Center. Not only are data available via this web-based system in real time, allowing rapid and simple receipt and access, but a built in email system allows for confidential communication among all investigators and coordinators working within the study's data management system.

D. Angiographic Core Laboratory

The Clinical Coordinating Center will randomly select 1500 cine angiograms of initial procedures for review by the core laboratory. Copies of cine CD's will be mailed to the Angiography Core for review. Angiography Core staff will enter angiographic outcomes data directly into Sextant for this subset of patients.

VII. Timetable for initiating and completing the study

A pilot project is on-going in Alabama. Recruitment is expected to begin in several states by May 2006. It will take ~ 6 months to get all sites up and running. Study recruitment is for 24 months, so that the entire project should be completed within ~30 months. If recruitment proves slower than anticipated, the project may require 36 months to complete.

VIII. Source and amount of funding

Our experience with application for Federal funding (NIH, AHCPR) and private foundation support for the first C-PORT primary PCI trial was frustrating and disappointing. This seemed to be related, at least in some measure, to the highly controversial (at the time) nature of the proposed project. The current trial is certainly not less controversial. In addition to low likelihood of funding a highly controversial project, the time frame for funding is so slow that a question which need urgent response – before the procedure becomes essentially accepted – requires a faster funding response, as well.

Application for funding from drug and device companies is possible, but the constraints required of research performed under such funding mechanisms and the potential for significant conflict of interest (since these same companies are selling product to the very institutions and physicians supported) is best avoided if possible.

We believe that modest funding from the participating sites is the best way to obtain funding rapidly and with minimal conflict of interest. The project cost is $52,500 in the first and second year per center. This will allow for support of the necessary Coordinating Center personnel, data collection and management infrastructure, angiographic core laboratory and other necessary costs. The personnel cost of data collection itself, is borne by the participating hospital.

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